FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting

December 7, 2011

NDA 202324
Axitinib (Inlyta®)
Pfizer, Inc.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the Axitinib NDA with the Applicant's proposed indication "for treatment of patients with advanced renal cell carcinoma" to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1 Proposed Indication

"Axitinib is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma."

2 Executive Summary

This NDA submission is based on a single efficacy study, A4061032 (AXIS trial), in 723 patients with advanced renal cell carcinoma (RCC) who had failure of one prior therapy.

A4061032 (AXIS) was a randomized, controlled, open-label, multicenter Phase 3 trial comparing axitinib to sorafenib as second-line systemic therapy in patients with metastatic renal cell carcinoma. Patients were randomized to receive either axitinib 5 mg po BID or sorafenib 400 mg po BID. The primary efficacy endpoint was PFS as assessed by an Independent Review Committee consisting of two blinded radiologists.

Efficacy
The median PFS was 6.7 months (95% CI 6.3-8.4) for axitinib and 4.7 months (95% CI 4.6-5.6) for sorafenib, with a hazard ratio of 0.67 (95% CI 0.55-0.81).

Safety
The safety profile of axitinib is comparable to that of other drugs in the same class of small molecule inhibitors of the VEGF pathway in terms of the types of adverse events observed. Common adverse events include diarrhea, nausea, fatigue, asthenia, hypertension and dermatologic adverse events. Less common serious adverse events include arterial and venous thrombotic events, gastrointestinal perforation, bleeding events, hypothyroidism, dysphonia, proteinuria and reversible posterior leukoencephalopathy syndrome.

3 Issues with the submission

FDA seeks advice from the ODAC members on the following issues:

Issue #1: PFS benefit driven by the subset of cytokine-treated patients
The PFS benefit is driven by the subset of patients who were treated with cytokines as first-line systemic treatment where the difference in median PFS was 5.6 months. The difference in median PFS for patients previously treated with sunitinib was 1.4 months.

ODAC advice is sought on whether the issue of the PFS benefit being driven by a subset of patients that is likely to be scarce in the United States and the more

meager PFS benefit in patients previously treated with sunitinib would affect the overall benefit:risk assessment.

Issue #2: Benefit:risk ratio

ODAC advice is sought on whether the benefit:risk ratio is favorable for axitinib treatment in patients with advanced RCC after failure of a first-line systemic therapy.

4 Background

4.1 Renal Cell Carcinoma

Renal cell carcinoma (RCC) is the seventh leading cancer type in men and the eighth leading cancer type in women, with an estimated total of 58,240 new cases and 13,040 deaths due to RCC in 2010.[1] Localized RCC can be treated with surgery with excellent long-term survival results. However, the prognosis for patients with locally advanced or metastatic disease remains poor, with median overall survival prior to the introduction of Surgery and traditional chemotherapy have not played a role in advanced or metastatic RCC, as their use has not been shown to affect survival in this population. Cytokines such as interferon-α (IFN-α) and interleukin-2 (IL-2) have response rates ranging from 7% to 23%,[2,3] and high-dose IL-2 has been shown to induce durable complete responses in approximately five percent of treated patients.[4] However, the toxicity associated with both of these agents has diminished their use, especially with the newer agents that have been developed in the last decade.

4.2 Advanced RCC Treatment

In the past six years, the treatment options for patients with advanced RCC have increased from IFN-α and IL-2 to six new agents with two different modes of actions: vascular endothelial growth factor receptor (VEGF-R) inhibitors sorafenib, sunitinib and pazopanib and VEGF antibody bevacizumab; and mammalian target of rapamycin (mTOR) inhibitors temsirolimus and everolimus.

Table 1: Currently Available Treatments for Advanced Renal Cell Carcinoma*

Drug Name	Trial Type	Approval Date	Approval Basis	Survival Benefit?
Sorafenib	Randomized, double-blind, compared to placebo in patients with one prior systemic therapy†	December 2005 Full approval	PFS	No
Sunitinib	Two single-arm trials in patients with cytokine-refractory disease Randomized, double-blind, compared to IFN-α in previously untreated patients	January 2006 Accelerated approval February 2007 Full approval	ORR, DOR PFS	No No
Temsirolimus	Randomized, open-label, compared to IFN-α, in previously untreated patients with poor prognostic factors	May 2007 Full approval	OS (2nd PFS)	Yes
Everolimus	Randomized, double-blind, compared to placebo, in patients with RCC treated previously with sorafenib or sunitinib	March 2009 Full approval	PFS	No
Bevacizumab+ IFNα	Randomized, double-blind, compared to IFNα alone in previously untreated patients	July 2009 Full approval	PFS	No
Pazopanib	Randomized, double-blind, compared to placebo in treatment-naïve patients or patients (54%) with one prior cytokine regimen (46%)	October 2009 Full approval	PFS	No

*All of the above treatments are indicated for the treatment of advanced RCC with the exception of everolimus, which is indicated for the treatment of advanced RCC after failure of treatment with sunitinib or sorafenib.
†Approximately 83% of patients had received cytokine therapy; the remaining 17% received chemotherapy or hormonal agents as prior therapy.

Sorafenib was the first of these agents to receive marketing approval in December 2005. It was approved on the basis of a randomized trial in patients with advanced RCC who had received one prior systemic therapy in which a PFS advantage of 167 days versus 84 days in the placebo arm was demonstrated. Approximately 83% of patients had received a cytokine regimen as prior therapy, and the remainder of patients had received a variety of chemotherapeutic agents or hormonal agents. Although overall survival was a co-primary endpoint, the PFS results prompted submission of these results given the lack of therapy options. Regular approval was given, and overall survival results were affected as the vast majority of patients from the placebo arm crossed over to treatment with sorafenib; thus, no survival advantage ever has been demonstrated for sorafenib in advanced RCC, whether in the first-line or second-line setting.

The second targeted agent that was approved in January 2006, sunitinib, initially received accelerated approval on the basis of response rates in single-arm trials. Two single-arm trials in patients with cytokine refractory RCC demonstrated response rates of 34-37%. Full approval was given based on a randomized trial in treatment-naïve patients with advanced RCC in which sunitinib demonstrated a PFS advantage of 47 weeks compared to 22 weeks in the IFN-α arm. Again, an overall survival benefit was not demonstrated, and crossover of placebo patients to the sunitinib arm was permitted.

The third targeted agent, temsirolimus, is the only agent that has shown an overall survival advantage in this disease. Temsirolimus was compared to IFN-α in previously untreated patients with advanced RCC and poor prognostic factors; median OS in the temsirolimus group was 10.9 months versus 7.3 months in the IFN- α group.

Bevacizumab in combination with IFN-α was approved in July 2009 based on a randomized trial in previously untreated patients with advanced RCC comparing the combination to IFN-α alone. The median PFS was 9.2 months in the combination arm versus 4.2 months in the IFN- α arm. Final OS results reported in 2010 did not show a difference in OS between the two arms.

Pazopanib is the most recent addition to the armamentarium in December 2009. Full approval was granted on the basis of a randomized trial in patients who had received no prior therapy or one prior cytokine-based systemic regimen to pazopanib or placebo. Median PFS was 9.2 months in the pazopanib group and 4.2 months is the placebo group; OS data was not mature at the time of approval, and study design allowed for crossover at the time of progression for placebo-treated patients. Thus, this trial also was not designed to rigorously compare OS between the two arms.

Everolimus is the only approved agent that is specifically indicated for a second-line indication. Everolimus was compared to placebo in patients who had progressed after sunitinib or sorafenib, with a median PFS of 4.9 months compared to 1.9 months in the placebo arm; overall response rate was 2% in the everolimus arm and 0 in the placebo arm. The interim analysis of OS showed no difference between the treatment arms. The trial allowed crossover of placebo patients on progression; as 109 of 139 patients on the placebo arm crossed over to everolimus, demonstration of an OS benefit would be unlikely.

4.3 Second-line treatment advanced RCC

All of the approvals for advanced RCC since 2005 have been given the broad indication of advanced RCC, except everolimus, which received a second-line indication. Most of the trials to support these broad indications were conducted in treatment-naïve patients; however, the pivotal trials for both sorafenib and pazopanib had mixed populations of treatment-naïve patients, patients who had received cytokine regimens, or patients who had received other regimens such as traditional chemotherapies or hormonal agents.

The appropriate order of targeted therapies to use in advanced RCC is not known. Everolimus is the only agent to be studied in a randomized trial after therapy with a VEGF pathway inhibitor. Recently published trials in second-line advanced RCC after initial treatment with a VEGF pathway inhibitor are single-arm trials and/or retrospective case series.

4.3.1 Primary endpoints for prior approvals

Table 1 above summarizes the primary endpoints that have been used for drug approvals for the treatment of patients with advanced RCC. The vast majority has used PFS for full approval; temsirolimus demonstrated an OS benefit.

The appropriate clinical trial endpoint in the second-line setting is unclear. The full approvals for targeted agents in advanced RCC based on PFS were in a regulatory environment in which the treatment options of IL-2 and IFN-α were not used commonly for first-line therapy, as demonstrated by the advice given by the Oncologic Drugs Advisory Committee that randomized trials with a placebo arm were neither unethical nor would they have difficulty in accruing patients. However, in the current setting there are multiple choices for first-line agents. Given the shorter expected duration of OS in the second-line setting, the use of OS as the primary endpoint in clinical trials used to support a marketing application could be considered.

4.4 Major Regulatory Milestones for Axitinib Development

The major regulatory milestones for axitinib development in advanced RCC are described in Table 2 below.

Table 2: Key Regulatory Activities Related to Clinical Development

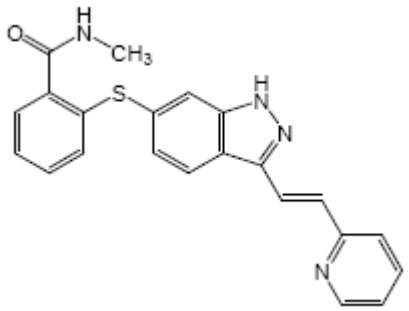
Milestone	Time	Details
IND 63662 activated	December 2001	• No significant initial deficiencies
End-of-Phase 2 meeting	May 2007	• Randomized, Phase 3 trial in advanced RCC in second-line setting with sorafenib as comparator arm with blinded IRC-assessed primary efficacy endpoint discussed • Sponsor indicated second-line indication would be sought based on design of Phase 3 trial • FDA recommended overall survival as primary endpoint and discouraged interim analyses for efficacy based on progression-free survival
Special Protocol Assessment	January 2008	SPA denied based on all of the following: PFS as primary endpoint, potential interim efficacy analyses by the DMC, inadequate case report forms, inadequate safety monitoring during the trial and continued treatment despite documented disease progression
Special Protocol Assessment	April 2008	SPA granted with caveat that improvements in the primary endpoint of PFS must be both clinically and statistically significant
Pre-NDA meeting	January 2010	• Sponsor proposed “advanced RCC” for the indication; FDA noted that the indication will reflect the population studied • Sponsor indicated that a second ongoing Phase 3 trial in second-line advanced RCC may be amended to include treatment-naïve patients; FDA encouraged powering the trial to detect a realistic improvement in OS
NDA submission	April 2011	Standard review designated

5 Drug Description

Axitinib is chemically designated as *N*-methyl-2-[3-((*E*)-2-pyridin-2-yl-vinyl)-1*H*-indazol-

400 6-ylsulfanyl]-benzamide. The molecular formula is $C_{22}H_{18}N_4OS$, and the molecular weight is 386.47 Daltons. The structural formula is shown in Figure 1.

Figure 1: Structural Formula of Axitinib



6 Study A4061032

Study Title: Axitinib (AG-013736) as Second Line Therapy for Metastatic Renal Cell Cancer: AXIS Trial.

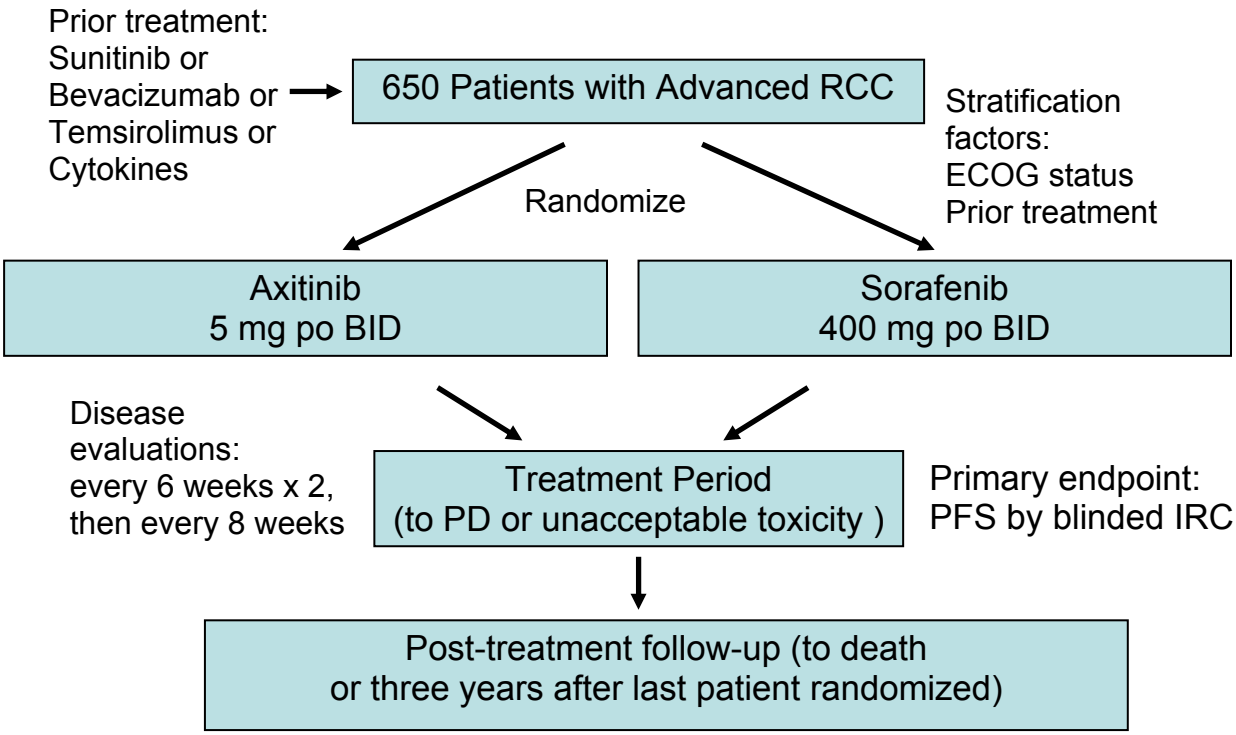
Objectives:

- **The primary objective** of the study was to compare the PFS of patients with mRCC receiving axitinib versus sorafenib following failure of one prior systemic first-line regimen containing one or more of the following: sunitinib, bevacizumab + IFN-α, temsirolimus, or cytokine(s).

6.1 Study Design

A4061032 (AXIS) was a randomized, controlled, open-label, multicenter Phase 3 trial comparing axitinib to sorafenib as second-line systemic therapy in patients with metastatic renal cell carcinoma.

Figure 2 Study design schema



6.2 Study Drug administration and schedule

Following the screening period (of up to 28 days), eligible patients were randomized to receive either:

- Arm A: axitinib administered 5 mg po BID
- Arm B: sorafenib administered 400 po mg BID

The axitinib dose could be escalated or decreased depending on the adverse events experienced by the patient. The dose could be escalated if a patient experienced no AEs related to study drug above CTCAE Grade 2 for a consecutive 2-week period by 1 dose level to a maximum of 10 mg BID (unless the patient's BP was >150/90 mm Hg or the patient was receiving antihypertensive medication). The clinical judgment of the treating physician was exercised when increasing the axitinib dose.

Table 3: Axitinib Dose Levels

Dose Level	Dose
+2	10 mg BID
+1	7 mg BID
0 (Starting Dose)	5 mg BID
-1	3 mg BID
-2	2 mg BID

6.3 Duration of treatment

Patients were treated until the development of progressive disease, unacceptable toxicity, protocol deviation, and/or consent withdrawal. Patients who withdrew from the study for any reason could start other anti-cancer treatments.

6.4 Study Endpoints

The primary efficacy endpoint PFS as assessed by an Independent Review Committee (IRC).

Secondary efficacy endpoints included overall survival, overall response rate, duration of response and PFS as assessed by investigator.

6.5 Major eligibility criteria

1. Histologically or cytologically confirmed mRCC with a component of clear cell subtype.
2. Measurable disease.
3. Progressive disease per Response Evaluation Criteria in Solid Tumors (RECIST, Version 1.0) after one prior systemic first-line regimen for mRCC. The prior regimen had to have contained one or more of the following: sunitinib, bevacizumab + IFN-α, temsirolimus, or cytokine(s).
4. ECOG performance status of 0 or 1.
5. No evidence of pre-existing uncontrolled hypertension as documented by 2 baseline blood pressure (BP) readings. Patients whose hypertension was controlled by antihypertensive therapies were eligible.

6.6 Primary endpoint evaluation

Efficacy: The primary endpoint for the trial was PFS as assessed by an Independent Review Committee (IRC). Radiographic images were evaluated by a blinded IRC to assess tumor status and to confirm response and progression of disease according to RECIST v1.0. The radiographic images documenting efficacy endpoints were

made available to allow the independent review. Two independent reviewers read scans. Differences between the two independent reviewers were to be resolved by a third reviewer (adjudicator) for final determination.

PFS was defined as the time from randomization to first documentation of objective tumor progression or to death due to any cause, whichever occurred first. If tumor progression data included more than 1 date, the first date was used. A stratified (i.e., ECOG PS and prior therapy) log-rank test (1-sided, α=0.025) was used to compare PFS between the 2 treatment arms. The median event time for each treatment arm and corresponding 2-sided 95% CI for the median were provided for PFS. The HR and its 95% CI were estimated.

6.7 Safety Evaluation

The Phase 3 trial A4061032 included safety assessments at baseline, every two weeks in the first cycle, on day 1 ± four days of every subsequent 28-day cycle, at the end of treatment and at a follow-up visit (28 days after the last dose). Serious adverse events that had not recovered completely by the end of treatment were to be followed until resolution.

At baseline, safety assessments included medical, oncologic, and surgical history, vital signs, blood pressure, physical examination, laboratories (hematology, chemistries, liver enzymes and function, thyroid function, urine evaluation, pregnancy test), assessment of ECOG PS and ECG. Safety assessments performed at the start of each cycle were the same as at baseline, except thyroid function tests were required every other cycle starting at cycle 4. Post-treatment follow-up for survival was to occur every 3 months until at least three tears after randomization of the last patient.

AEs were coded by body system using a medical dictionary for regulatory authorities (MedDRA®) and were graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) scale, Version 3.0.

7 Study Results

Study results were based on the database cut-off date of August 31, 2010.

7.1 Patient Population

Efficacy: The efficacy analysis was based primarily on the intent-to-treat population of 723 patients in the A4061023 trial.

Safety: The safety analysis was performed primarily on the 714 patients who received ≥ 1 dose of axitinib or sorafenib in the A4061023 trial (see section 7.3).

7.2 Efficacy (Study A4061032)

7.2.1 Patient characteristics

Table 4 lists patient demographics and disease characteristics, which were well matched between arms.

Table 4: Patient Baseline Characteristics

	Axitinib N=361	**Sorafenib N=362**
Median Age, Years (Min, Max)	61 (20, 82)	61 (22, 80)
Sex (%)		
Male	265 (73.4)	258 (71.3)
Female	96 (26.6)	104 (28.7)
ECOG PS (%)		
0	192 (54)	200 (55.2)
1	162 (44.9)	160 (44.2)
>1	1 (<1)	0
Geographic Region		
North America	88 (24.4)	98 (27.1)
Europe	187 (51.8)	170 (47)
Asia	73 (20.2)	79 (21.8)
Other	13 (3.6)	15 (4.1)
Race		
White	278 (77)	269 (74.3)
Black	1 (<1)	4 (1.1)
Asian	77 (21.3)	81 (22.4)
Other	5 (1.4)	13 (3.6)
MSKCC Risk Group		
Favorable	158 (43.8)	148 (40.9)
Intermediate	199 (55.1)	210 (58)
Poor	4 (1.1)	4 (1.1)

Table 5 shows the systemic treatment patients had received for RCC prior to the enrollment. Sunitinib and cytokines were the two most frequent prior treatments patients received for mRCC prior to enrolling in this trial. However, in North America and Europe, patients were almost twice as likely to receive sunitinib as prior treatment than cytokines (see Table 6).

Table 5: Prior Treatment

Prior Treatment	Axitinib (N=361) n (%)	Sorafenib (N=362) n (%)
Sunitinib	194 (53.7)	195 (53.9)
Bevacizumab	29 (8)	30 (8.3)
Temsirolimus	12 (3.3)	12 (3.3)
Cytokine	126 (34.9)	125 (34.5)

Table 6: Prior treatment in North America and Europe

Treatment	North America N=186	Europe N=357	Total N=543
Sunitinib	126 (67.7)	180 (50.4)	306 (56.4)
Cytokine	37 (19.9)	125 (34.5)	162 (29.8)

7.2.2 Primary endpoint result --- PFS

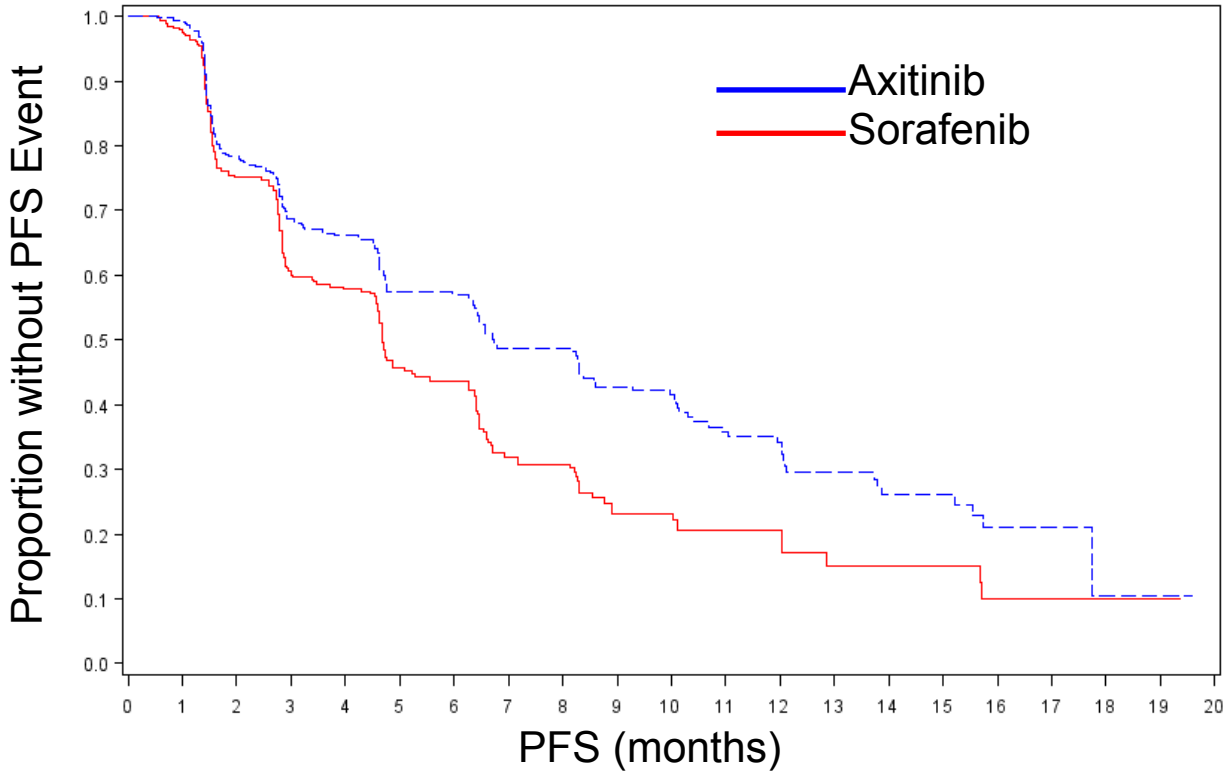
PFS as assessed by the IRC was the primary efficacy endpoint. At the time of the final analysis, 402 patients had experienced a PFS event. The analysis for PFS is shown in Table 7 and Figure 3 below.

Table 7: Progression-free Survival by IRC

	Axitinib N=361	Sorafenib N=362
Number of patients with progression (%)	180 (49.9)	200 (55.2)
Number of patients with deaths (%)	12 (3.3)	10 (2.8)
PFS event (%)	192 (53.2)	210 (58)
Median PFS in months (95% CI)	6.7 (6.3-8.4)	4.7 (4.6-5.6)
Hazard ratio (95% CI)[1]	0.67 (0.55-0.81)	
P-value[2]	<0.0001	

[1]Based on Proportional Hazards model stratified by ECOG PS and prior therapy.
[2]Based on one sided log rank test stratified by ECOG PS and prior therapy.

Figure 3: Kaplan-Meier Plot of Progression-free Survival



The applicant performed multiple subpopulation analyses, including PFS results according to the stratification factor of prior systemic therapy. For prior sunitinib or cytokine therapy, results are summarized in Table 8 below. For prior bevacizumab or temsirolimus, the number of patients was too small in these two groups to permit an analysis with any reliability. The difference between arms for median PFS in patients previously treated with cytokines is 5.6 months, whereas the difference for patients previously treated with sunitinib is 1.4 months.

Table 8: Progression-free Survival Stratified by Prior Treatment

	Axitinib (N=361)	**Sorafenib (N=362)**
PFS events (%) Sunitinib Cytokine	 117 (32.4) 50 (13.9)	 120 (33.1) 69 (19.1)
Median PFS in months (95% CI) Sunitinib Cytokine	 4.8 (4.5-6.4) 12.1 (10.1-13.9)	 3.4 (2.8-4.7) 6.5 (6.3-8.3)
Hazard ratio (95% CI)[1] Sunitinib Cytokine	 0.74 (0.57-0.96) 0.47 (0.32-0.68)	
P-value[2] Sunitinib Cytokine	 0.011 <0.0001	

[1]Based on Proportional Hazards model stratified by ECOG PS.
[2]Based on one sided log rank test stratified by ECOG PS.

Figure 4: PFS in Patients Previously Treated with Cytokines

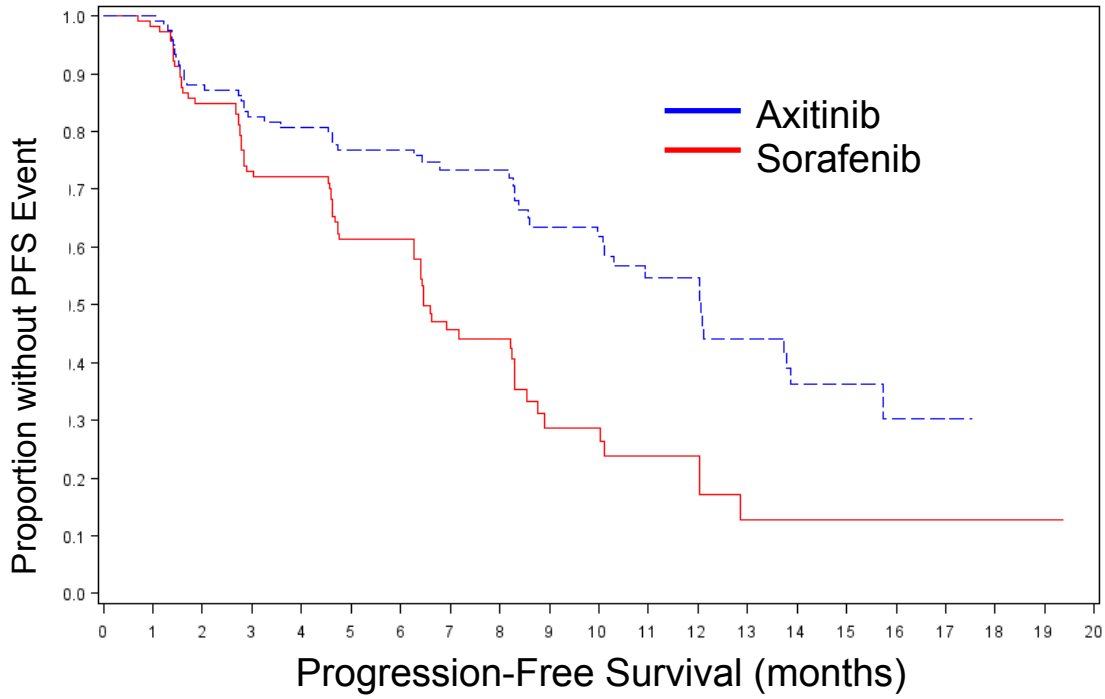
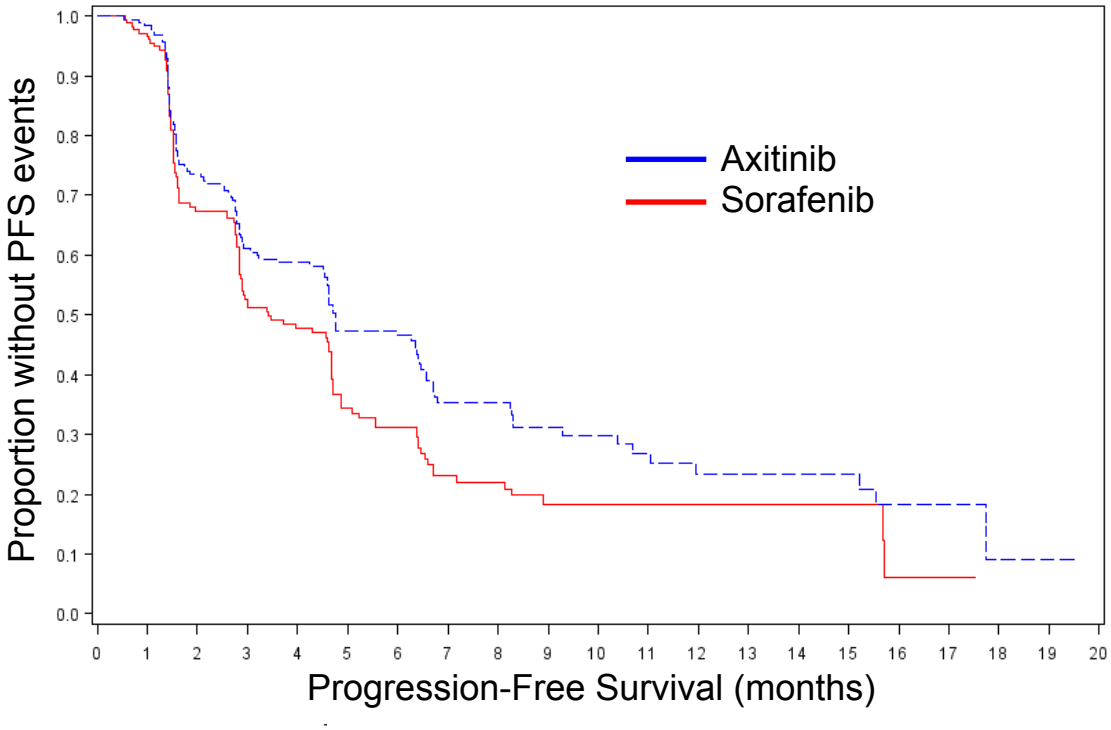


Figure 5: PFS in Patients Previously Treated with Sunitinib



7.2.3 Key Secondary Endpoints

Overall Survival

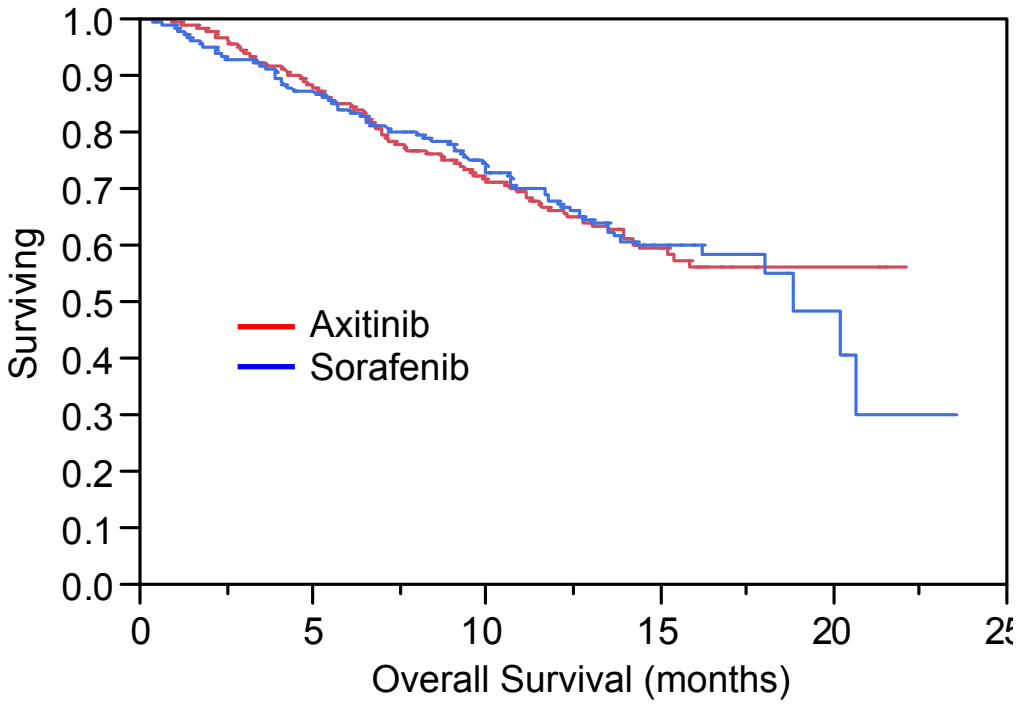
At the time of the NDA submission, the interim analysis for overall survival occurred at 223 events, which is approximately 53% of the events needed for the final OS analysis. There were more deaths overall in the axitinib arm. As seen in Table 9 and Figure 6 below, there was no difference in OS at the interim analysis. The final analysis for OS is expected in the first quarter of 2012.

Table 9: Overall Survival

	Axitinib N=361	**Sorafenib N=362**
Deaths (%)	113 (31.3)	110 (30.4)
Median OS (months)	NR (15.9, NE)	18.9 (18, NE)
HR (95% CI)[1]	1.008 (0.77-1.31)	
p-value[2]	0.53	

[1]Based on Proportional Hazards model stratified by ECOG PS and prior therapy.
[2]Based on one sided log rank test stratified by ECOG PS and prior therapy.

Figure 6: Kaplan-Meier Plot of Overall Survival



There was no crossover in this study from the sorafenib to axitinib. Patients were permitted to remain on treatment post-progression at the discretion of the treating physician. On the axitinib arm, 50/187 (26.7%) patients who progressed remained on treatment more than 28 days after progression, whereas on the sorafenib arm 74/214 (34.6%) patients continued on treatment more than 28 days after progression. The applicant also collected post-progression treatment data for patients on the trial, which is summarized in the table below. The table includes only treatments for which ≥1% of patients on either arm received it.

Table 10: Post-progression Systemic Therapy

Post-progression Treatment	Axitinib N=361	Sorafenib N=362
Any follow-up systemic therapy (%)	101 (28)	133 (36.7)
Bevacizumab	10 (2.8)	19 (5.2)
Everolimus	55 (15.2)	73 (20.2)
Interferon	4 (1.1)	8 (2.2)
Pazopanib	8 (2.2)	9 (2.5)
Sirolimus	14 (3.9)	18 (5)
Sorafenib	29 (8)	18 (5)
Sunitinib	10 (2.8)	30 (8.3)
Temsirolimus	0	8 (2.2)

Response Rate and Duration of Response

The response rate (CR + PR) by blinded IRC assessment was 70 (19.4%) patients in the axitinib arm and 34 (9.4%) patients in the sorafenib arm. There were no CRs in either arm. Among patients previously treated with sunitinib, 22 patients on the axitinib arm had a PR compared to 15 on the sorafenib arm. Among patients previously treated with a cytokine regimen, 41 patients on the axitinib arm had a PR compared to 17 on the sorafenib arm. The median duration of response was 11 months (7.4, NE) in the axitinib arm and 10.6 months (8.8, 11.5) in the sorafenib arm.

7.3 Safety

7.3.1 Safety population

Table 11 lists all completed studies submitted in this application. Patients from study A4061032 form the core population for the safety analysis of axitinib.

Table 11: Summary of Axitinib Trials in Safety Analysis

Study #	Population	Design	Dose (mg B.I.D.)	# Any Axitinib	# Axitinib 5 mg B.I.D.
A4060010	Advanced Solid Tumors	Dose Escalation/Food Effects	2-30 QD to BID	36	20
A4061011	Advanced NSCLC	Activity	5	32	32
A4061012	2nd-line Advanced RCC after Cytokine	Activity	5	52	52
A4061014	Advanced Thyroid Cancer	Activity	5	60	60
A4061015	Metastatic Melanoma	Activity	5	32	32
A4061022	Advanced Solid Tumors	Activity	5	12	12
A4061023	2nd-line Advanced RCC after Sorafenib	Activity	5	62	62
A4061032	2nd-line Advanced RCC	Phase 3 Axitinib vs. Sorafenib	5	359	359
A4061035	2nd-line Advanced RCC after Cytokine	Activity	5	64	64
A4061044	Advanced Solid Tumors	PK	5	6	6
Total Exposed				**715**	**715**
ISS Total					**715**
ISS RCC					**545**

7.3.2 Drug Modifications/Discontinuations

Diarrhea and hypertension accounted for the majority of dose modifications on the axitinib arm, while sorafenib patients more often had dose modifications for palmar-plantar erythrodysasthesia syndrome and diarrhea. Hypothyroidism, upper abdominal pain, dysphonia and pharyngitis each accounted for dose modification in at least 3 patients on the axitinib arm but none on the comparator arm.

More patients discontinued treatment on the sorafenib arm than on the axitinib arm. The primary reasons for treatment discontinuations were disease progression (44.6% on axitinib versus 50.7% on sorafenib); adverse events (6.1% on axitinib versus 9.3% on sorafenib); death (3.3% on axitinib versus 3.7% on sorafenib); and patient refusing further treatment (2.8% on axitinib versus 2% on sorafenib).

7.3.3 Adverse Events

The adverse event profile for axitinib is similar to other drugs in the same class of small molecule inhibitors of the VEGF pathway. This includes common adverse events such as diarrhea, nausea, hypertension, fatigue and dermatologic AEs as well as less common AEs such as arterial and venous thrombotic events, gastrointestinal perforation, bleeding events, hypothyroidism, proteinuria and reversible posterior leukoencephalopathy syndrome. Axitinib does not appear to have the same degree of liver enzyme elevation and potential for liver failure as some other VEGF pathway small molecule inhibitors.

The most common adverse events (≥10% on either arm) in A4061032 are shown in Table 12. Among these, the most common were diarrhea, hypertension, fatigue, decreased appetite and nausea. In general, axitinib had higher rates of gastrointestinal events, fatigue, asthenia, hypertension, hypothyroidism and dysphonia than sorafenib. However, axitinib had lower rates of dermatologic AEs and anemia than sorafenib.

Table 12: Common Adverse Events on A4061032

	Axitinib N=359		**Sorafenib N=355**	
	Gr 1-4 (%)	Gr 3-4 (%)	Gr 1-4 (%)	Gr 3-4 (%)
Blood and lymphatic system disorders				
Anemia	17 (4.7)	4 (1.1)	44 (12.4)	14 (3.9)
Endocrine disorders				
Hypothyroidism	69 (19.2)	1 (0.3)	30 (8.5)	0
Gastrointestinal disorders				
Abdominal pain	54 (15)	10 (2.8)	38 (10.7)	3 (0.8)
Constipation	74 (20.6)	4 (1.1)	76 (21.4)	3 (0.8)
Diarrhea	197 (54.9)	38 (10.6)	192 (54.1)	26 (7.3)
Dyspepsia	36 (10)	0	9 (2.5)	0
Nausea	117 (32.6)	9 (2.5)	80 (22.5)	4 (1.1)
Stomatitis	55 (15.3)	5 (1.4)	44 (12.4)	1 (0.3)
Vomiting	86 (24)	12 (3.3)	63 (17.7)	3 (0.8)
General disorders and administration site conditions				
Asthenia	75 (20.9)	19 (5.3)	51 (14.4)	9 (2.5)
Fatigue	146 (40.7)	41 (11.4)	114 (32.1)	18 (5.1)
Mucosal inflammation	55 (15.3)	5 (1.4)	44 (12.4)	2 (0.6)
Pyrexia	27 (7.5)	3 (0.8)	38 (10.7)	1 (0.3)
Investigations				
Weight decreased	89 (24.8)	8 (2.2)	74 (20.8)	5 (1.4)

	Axitinib N=359		Sorafenib N=355	
Metabolism and nutrition disorders				
Decreased appetite	123 (34.3)	17 (4.7)	103 (29)	13 (3.7)
Musculoskeletal and connective tissue disorders				
Arthralgia	56 (15.6)	7 (1.9)	39 (11)	5 (1.4)
Back pain	51 (14.2)	9 (2.5)	51 (14.4)	6 (1.7)
Pain in extremity	46 (12.8)	2 (0.6)	50 (14.1)	2 (0.6)
Nervous system disorders				
Dysgeusia	39 (10.9)	0	29 (8.2)	0
Headache	53 (14.8)	2 (0.6)	40 (11.3)	0
Renal and urinary disorders				
Proteinuria	41 (11.4)	11 (3.1)	26 (7.3)	6 (1.7)
Respiratory, thoracic and mediastinal disorders				
Cough	59 (16.4)	3 (0.8)	63 (17.7)	2 (0.6)
Dysphonia	114 (31.8)	0	50 (14.1)	0
Dyspnea	57 (15.9)	11 (3.1)	46 (13)	11 (3.1)
Skin and subcutaneous tissue disorders				
Alopecia	14 (3.9)	0	117 (33)	0
Dry skin	36 (10)	0	38 (10.7)	0
Erythema	9 (2.5)	0	36 (10.1)	1 (0.3)
Palmar-plantar erythrodysaesthesia syndrome	98 (27.3)	18 (5)	181 (51)	57(16.1)
Pruritus	24 (6.7)	0	44 (12.4)	0
Rash	45 (12.5)	1 (0.3)	112 (31.5)	14 (3.9)
Vascular disorders				
Hypertension	146 (40.7)	56(15.6)	104 (29.3)	39 (11)

Serious Adverse Events (SAEs)

Nonfatal serious adverse events occurred in 34.8% of patients on the axitinib arm and 32.7% on the sorafenib arm. SAEs that occurred in ≥1% of patient on either arm are summarized in the table below.

Table 13: Nonfatal Serious Adverse Events (≥1% on Either Arm)

	Axitinib N=359	Sorafenib N=355
Any SAE (%)	125 (34.8)	116 (32.7)
Disease progression	27 (7.5)	16 (4.5)
Dehydration	9 (2.5)	1 (<1)
Diarrhea	8 (2.2)	5 (1.4)
Pyrexia	7 (1.9)	3 (<1)
Dyspnea	5 (1.4)	3 (<1)
Pulmonary Embolism	5 (1.4)	1 (<1)
Pneumonia	4 (1.1)	4 (1.1)
Pneumothorax	4 (1.1)	1 (<1)
Fatigue	4 (1.1)	0
Pleural Effusion	3 (<1)	5 (1.4)
Pain	2 (<1)	5 (1.4)
General Physical Health Deterioration	2 (<1)	4 (1.1)
Myocardial Infarction	1 (<1)	4 (1.1)
Hypotension	1 (<1)	4 (1.1)
Anemia	0	4 (1.1)

7.3.4 Deaths

More total deaths occurred on the axitinib arm than on the sorafenib arm, and more deaths on the axitinib arm were associated with treatment-emergent adverse events than on the sorafenib arm (2.5% versus 1.1%). Deaths within 28 days of last drug dose were 9.7% on the axitinib arm and 6.5% on the sorafenib arm. All deaths occurring in the safety population are included in the table below.

Table 14: All Safety Population Deaths on A4061032

	Axitinib N = 359	Sorafenib N = 355
Total Deaths	113 (31.5%)	109 (30.7%)
Deaths within 28 Days of Last Dose	35 (9.7%)	23 (6.5%)
TEAEs	8 (2.2%)	5 (1.4%)
Progression	26 (7.2%)	14 (3.9%)
Other	1 (<1%)	4 (1.1%)
Unknown	1	2
Other Events	0	2
Deaths in follow-up*	78 (21.7%)	86 (24.2%)
TEAEs	0	0
Progression	65 (18.1%)	72 (20.3%)
Other	13 (3.6%)	14 (3.9%)
Unknown	3	7
Other Events†	10	7

*More than 28 days after last dose of study drug to clinical data cutoff of August 31, 2010.
† Other events on the axitinib arm included acute renal failure, acute myocardial infarction, cardiopulmonary failure, interstitial lung disease, intrapulmonary and intrabronchial bleeding, and respiratory hemorrhage.

Eight axitinib-treated patients and five sorafenib-treated patients experienced a Grade 5 TEAE other than disease progression within 28 days of the last dose of study drug.

8. Summary

This NDA submission is based primarily on a single randomized efficacy study, A4061032, in patients with advanced RCC after failure of one prior systemic regimen.

The difference in median PFS on this trial was approximately two months. However, the difference in median PFS for patients previously treated with cytokines was 5.6 months, whereas the difference in patients previously treated with sunitinib was 1.4 months. The PFS benefit likely will not translate to an OS benefit; at over half the events needed for the final analysis, the hazard ratio was 1.009. No sorafenib patients were crossed over to axitinib after progression. The response rate is 19.5% on the axitinib arm compared to 9.4% on the sorafenib arm. Although more than half the patients had received sunitinib and slightly over a third had received cytokines, there were more responses on the axitinib arm in patients previously treated with cytokines than patients previously treated with sunitinib.

The main toxicities were similar to other approved VEGF pathway inhibitors.

ODAC advice is sought on the whether the benefit:risk ratio is favorable for axitinib despite the efficacy being driven by a subset of patients who are rare in the United States.

9. References

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[4] Rosenberg SA, Lotze MT, Muul LM, et al.: A progress report on the treatment of 157 patients with advanced cancer using lymphokine-activated killer cells and interleukin-2 or high-dose interleukin-2 alone. N Engl J Med 316 (15): 889-97, 1987.